J Neurol (2008) 255:305–307
DOI 10.1007/s00415-007-0730-5

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Development of extensive brain lesions following interferon beta therapy in relapsing neuromyelitis optica and longitudinally extensive myelitis

Received: 23 June 2007
Received in revised form: 15 August 2007
Accepted: 5 September 2007
Published online: 21 November 2007

Sirs: Relapsing neuromyelitis optica (RNMO) is characterised by recurrent longitudinally extensive myelitis (RLEM) and severe optic neuritis [5, 7, 10, 14]. The effects of disease-modifying therapies, including interferon beta (IFNβ), have not been fully established in RNMO or RLEM [15]. The neuromyelitis optica immunoglobulin G (NMO-IgG) auto-antibody (Ab) is a marker for NMO [3], which binds to the aquaporin 4 (AQP4) water channel protein [2]. Anti-AQP4 antibody titres may have implications in diagnosing NMO [13]. We report two cases of RNMO or RLEM with anti-AQP4 Ab, in which extensive (tumefactive) brain lesions developed within 2 months after initiation of IFNβ-1b.

Case 1

A woman suffered two episodes of thoracic myelitis at age 38. At age 39, she visited our clinic with optic neuritis of the right eye. Magnetic resonance imaging (MRI) showed T2-hyperintense spinal cord lesions in the T1–4 and T7–10 regions but no brain or cervical cord lesions. She was successfully treated with high-dose intravenous methylprednisolone (HIMP), and diagnosed with optic-spinal multiple sclerosis with RLEM. She began treatment with IFNβ-1b the following year, but after 2 months developed headache and fever. Neurological examination revealed left hemianopsia and hypoesthesia below the T6 level. Brain MRI revealed a large white matter lesion (Fig. 1). The patient tested positive for anti-AQP4 (8192X) [12], anti-Sjögren's Syndrome A (64X) and antinuclear Abs (320X), but had no

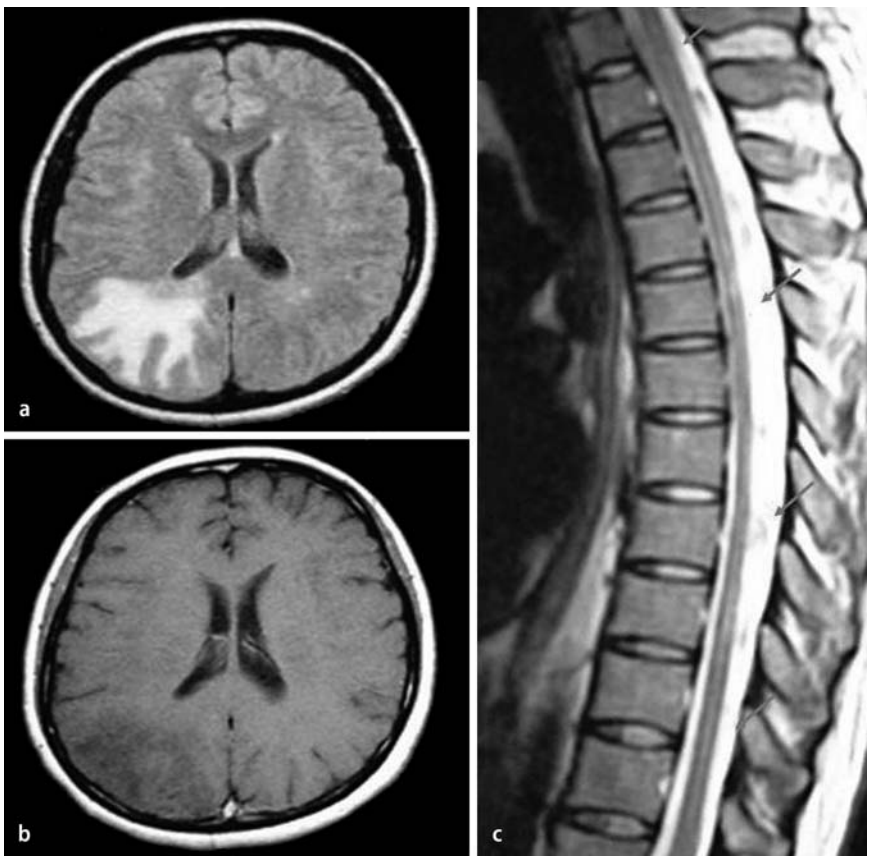

Fig. 1 Brain and spinal cord MRI in Case 1. **A, B** A large tumefactive lesion with oedema can be seen in the right parieto-occipital white matter. The lesion is FLAIR-high (**A**) and T1-low (**B**) in intensity. **C** Extensive T2-hyperintense spinal cord lesions are noted in regions T5–7 and T10–12

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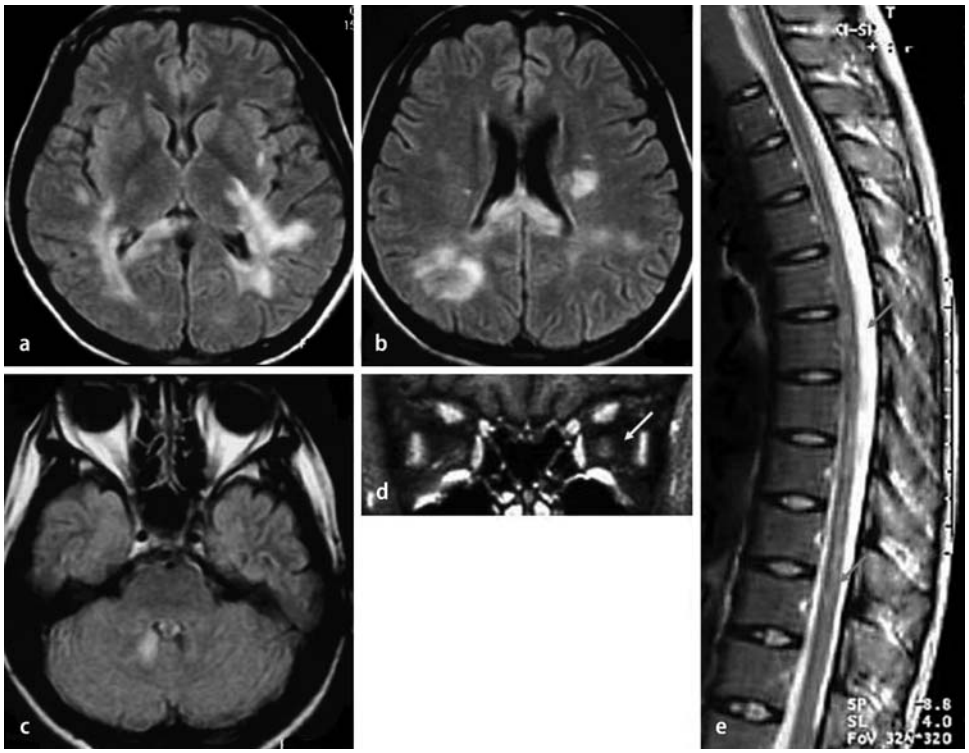

Fig. 2 Brain and spinal cord MRI in Case 2. Multiple FLAIR-hyperintense lesions are noted in the cerebral white matter, corpus callosum (**A, B**), and cerebellar white matter (**C**). **D** The left optic nerve is swollen and gadolinium-enhanced. **E** A longitudinally extensive T2-hyperintense spinal cord lesion is noted in the area T7–11

clinical symptoms of Sjögren's Syndrome or lupus. Cerebrospinal fluid (CSF) examination revealed no IgG oligoclonal bands (OB). The patient responded well to HIMP treatment. She was administered azathioprine (AZP) 50 mg daily for four years with no subsequent relapse.

Case 2

A 24-year-old woman had a 4-year history of RLEM. Two months after IFNβ-1b was initiated, she was admitted to hospital with confusion, severe headache, and vomiting with hiccups. Neurological examination revealed confusion, diminished left visual acuity, dysarthria, left leg weakness, and bilateral Babinski's sign. Brain MRI revealed lesions bilaterally in the cerebral white matter and cerebellum, and swelling of the left optic nerve with gadolinium enhancement (Fig. 2). CSF analysis found pleocytosis (13/mm^3), a total protein count of 47 mg/dl, and negative OB. The patient was seropositive for anti-cardiolipin immunoglobulin M (1.4 mg/dl) and anti-AQP4 Abs (512X) [12]. She was successfully treated with HIMP. Since then she has been treated with AZP 50 mg daily for five years with no new brain lesions.

These two patients were among 16 patients with RNMO or RLEM who have received IFNβ-1b in our hospitals. Both patients tested positive for auto-Abs associated with collagen diseases, and for anti-AQP4 Ab. Spinal MRI showed cord lesions longer than three vertebrae. Case 1 met the diagnostic criteria for NMO [15], while case 2 had RLEM. Strikingly, both developed brain lesions only after initiation of IFNβ therapy. Therefore, one must ask whether these lesions were related to IFNβ therapy. Selective optico-spinal involvement has been described as a unique feature of NMO. However, recent studies have revealed that some patients with RNMO and RLEM have brain lesions, some of which closely resemble those of our patients [1, 3, 8, 9, 11]. In our cases, brain lesions have not recurred since the initiation of AZP treatment. This supports a previous report of AZP and prednisolone combination therapy preventing relapse and reducing disability in NMO patients [4]. We suggest that the extensive lesions found in these patients soon after IFNβ-1b treatment may have been induced by transient upregulation of Th1 cytokines, as previously reported [6]. In addition to immunological alterations caused by IFNβ, anti-AQP4 Ab may have played a role in their pathogenesis. Larger-scale studies are needed to clarify the nature of this relationship.

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